Cyclosporin A and Transplant Coronary Diseas After H art Transplantation: Facts and Fiction

C9

A. Haverich, A. Costard-Jäckle, J. Cremer, G. Herrmann, and R. Simon

TRANSPLANT coronary disease (TCD) remains the single most important risk factor of death in heart transplant recipients surviving beyond the first postoperative year. Many clinical variables have been associated with the development of this complication, including older age of donor hearts, poor HLA matching, hyperlipidemia, hypertension, and others. Recently, chronic application of cyclosporin A (CyA) has been suggested to also represent a risk factor for TCD. This association was constructed on the basis of animal experiments, where significant impairment of endothelial and smooth muscle cell function was seen under CyA therapy.

THE PROBLEM

In our own series covering more than 400 heart transplants over a period of 8 years, TCD occurred in 11.2% of patients after 1 year, 17.9% after 2 years, and 28.6% after 3 years (Fig 1). In general, these coronary changes were asymptomatic and only detected by angiography. The linearized rate of yearly detection does reflect the experience of other larger transplant programs, which also report an annual occurrence of about 10%.

In our series as well as in others, TCD does have a significant impact on late death. As such, 62% of all fatalities beyond the first posttransplant year were directly related to TCD. A similar prevalence was observed in other series.[1] Graft dysfunction and rejection do account for more than 50% of late deaths in the registry of the International Society for Heart and Lung Transplantation.[2]

Considering the magnitude of the problem, intense search for risk factors precipitating TCD appears to be more than justified. Among many others, CyA treatment has been identified to cause impaired vasomotion, potentially resulting in TCD.

ANIMAL EXPERIMENTS

A large number of animal experiments have been conducted recently with the aim of understanding the pathomechanisms involved in CyA treatment and subsequent vessel wall dysfunction. Most studies were done using rings of the descending thoracic aorta in rats.

In one of these series, Auch-Schwelk et al[3] applied 60 mg/kg/d of CyA for 6 weeks before studying the aortic rings. At the time of harvesting, mean CyA blood level was 3376 ± 472 μg/L. Under these conditions, they were able to identify significantly diminished properties of endothelial and smooth muscle cell function in the aorta. Both endothelium-dependent and -independent vasodilation were severely impaired as demonstrated by the application of acetylcholine and nitroprusside sodium. Vasoconstriction induced by application of norepinephrine and potassium chloride, by contrast, was significantly enhanced. An identical experimental design applied by the same group in a subsequent study[4] showed that these impaired functional characteristics were reversible if the calcium channel blocking agent verapamil was given.

Rego et al[5] in a similar experiment could not find any significant changes in the vasomotor response of aortic rings following chronic application of CyA at a dose of 5 mg/kg/d. With administration of 10 mg/kg/d, by contrast, he could show the same alterations in constrictive and dilative properties of the rat aorta. Importantly, in their experiments, this pathologic response was reversible upon cessation of CyA therapy for 10 days.

Reversibility of changes was also noted in experiments by Xue et al,[6] who showed phentolamine to significantly reduce the pathologic response of CyA (dose 15 mg/kg/d)-treated rat aorta. Similarly, Gallego et al[7] identified L-arginine as a potent measure to counteract changes in aortic vasomotion following CyA application at very high doses (25 mg/kg/d). Their hypothesis of lack of endothelial-derived relaxing factor (EDRF) release in such vessels would be supported by the findings obtained after addition of the nitricoxyde (NO) donor L-arginine. This substance also reduced the abnormally increased calcium uptake in such aortic rings.

FINDINGS IN HUMANS

To compare these findings in animals with clinical data, O'Neil et al[8] performed an extremely attractive clinical experiment. They studied the endothelium-dependent and -independent vasodilation of human coronary arteries in vitro. Although the majority of specimens were normal vessels obtained from heart transplant recipients, three coronary arteries were taken from long-term CyA-treated patients at the time of heart-lung retransplantation for chronic lung rejection. Here, a completely normal response both to nitroglycerin and substance P was observed, even after 37 months of immunosuppression using CyA. They therefore concluded that CyA would not impair EDRF release even when applied long term.

From the Departments of Cardiovascular Surgery (A.H., A.C.-J., J.C.) and Cardiology (G.H., R.S.), University of Kiel, Kiel, Germany.

Address reprint requests to A. Haverich, Department of Cardiovascular Surgery, University of Kiel, Kiel, Germany.

0041-1345/94/$3.00/+0

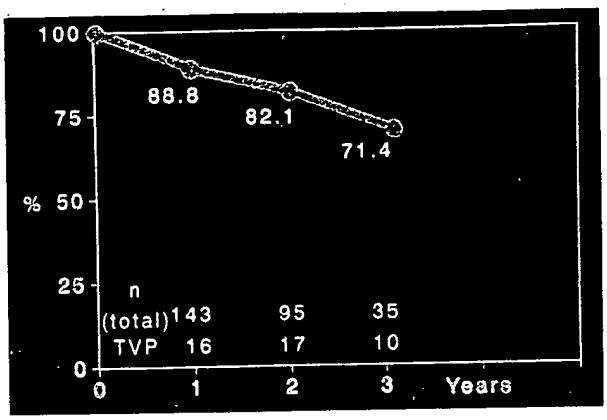

Fig 1. Linearized rate of freedom from TCD up to 3 years after orthotopic transplantation.

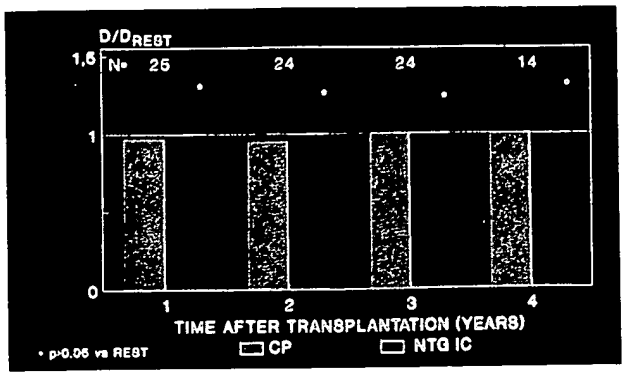

Fig 3. Response to nitroglycerin (NTG) in human coronary arteries 1 to 5 years after heart transplantation. Note significant increase in coronary artery diameter at all time intervals.

These data would support our own results on substance P—it triggered NO release in long-term surviving patients after heart transplantation. We were able to demonstrate a normal coronary artery response to substance P up to 5 years after orthotopic transplantation.[9] In patients with TCD, however, coronary vasodilation was significantly impaired (Fig 2). In addition, the Kiel group showed a continual normal response of coronary vasodilation following application of nitroglycerin and papaverine during yearly coronary angiography studies up to 4 years after transplantation (Fig 3).

There is further evidence that CyA may not be an independent risk factor for TCD. Five years ago, Gao et al[10] published long-term results of two cohorts of patients after heart transplantation. One group received conventional therapy including azathioprine (without use of CyA), the other group was maintained on a CyA-based immunosuppressive protocol. Linearized rates of freedom from TCD at 1, 3, and 5 years were 90, 70, and 58% in the azathioprine group and 93, 69, and 50% in the CyA group, respectively, without significant differences at the given intervals (Table 1). These data do reflect our own experience with an annual risk of about 10% of patients with de novo development of TCD (Fig 1). These findings neither support the concept of severely impaired coronary vasomotion in human heart transplant recipients on long-term treatment of CyA nor suggest that this drug promotes TCD by the mechanism of impaired vasomotion.

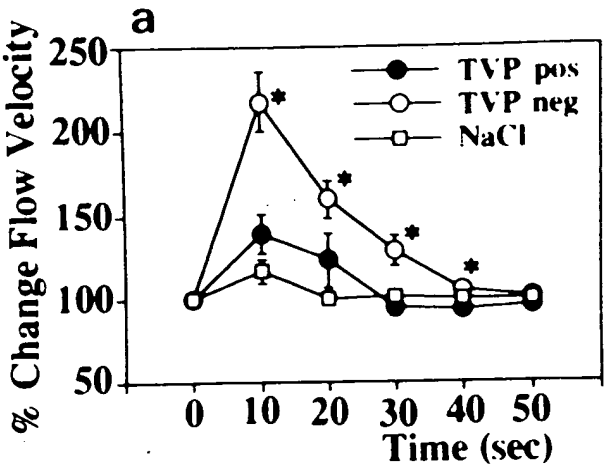

Fig 2. Effect of intracoronary application of substance P on flow velocity in heart transplant recipients with and without transplant vasculopathy (TVP).

SUMMARY AND CONCLUSIONS

From published data in the currently available literature on animal experiments, it can be concluded that CyA may be involved in the development of hypertension and renal dysfunction. These side effects are probably related to a disturbed vasomotor tone and a pathologic reaction to physiologic vasoconstrictive and vasodilative agents following administration of high doses of CyA. These effects are dose related and reversable and were undetected at clinically applied levels of immunosuppression. It therefore appears to be unlikely that this pathologic response is operative in precipitating or promoting TCD, which is supported by findings of in vivo and in vitro studies on human coronary arteries as well as by comparison of immunosuppressive protocols comparing series with and without application of CyA.

Chronic graft dysfunction, as depicted by late mortality in heart and isolated lung transplant recipients and by loss of kidney allograft survival, yields an annual rate of between 4

Table 1. Freedom From TCD at 1, 3, and 5 Years after Heart Transplantation Using Azathioprine (Aza)- and CyA-Based Immunosuppression

	Aza (%)	CyA (%)	*p*
1 y	89	86	n.s.
3 y	74	63	n.s.
5 y	58	50	n.s.

Note. There were no significant differences between groups (from Gao et al[10]).

and 6% per year. It is only in heart transplantation that TCD has been tried to be associated with CyA application. If CyA-related damage were to occur in coronary arteries independent from immunologic factors, the incidence of coronary disease should be similar in heart, lung, liver, and kidney transplants. This is not the case.

Although continuous investigation on the side effects of immunosuppressive agents is definitely necessary, we should concentrate our research activities on potential prophylactic and therapeutic measures to overcome the single most important risk factor of long-term surviving patients after solid organ transplantation: chronic rejection.

REFERENCES

1. Grattan MT, et al: JAMA 261:3561, 1989
2. Kriett JM, Kaye MP: J Heart Lung Transplant 10:491, 1991
3. Auch-Schwelk W, et al: J Cardiovasc Pharmacol 21:435, 1993
4. Götze S, et al: Eur Heart J 14(suppl x):1, 1993
5. Rego A, et al: Transplant Proc 20(suppl 3):572, 1988
6. Xue H, et al: Transplantation 43:715, 1987
7. Gallego MJ, et al: Circ Res 74:477, 1994
8. O'Neil GS, et al: Br Heart J 52:212, 1993
9. Mügge A, et al: J Am Coll Cardiol 21:163, 1993
10. Gao SZ, et al: Circulation 80 (suppl III):III-100, 1989